K110203

5.0 510(k) Summary

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As required by 21 CFR Section 807.92(c).

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Contact:	Russel K. Enns, Ph.D.
Date of Preparation:	April 6, 2011
Device:	
Trade name:	Xpert® *C. difficile/Epi*
Common names:	*C. difficile/Epi* Assay, *C. diff/Epi* Assay, and *Clostridium difficile* identification and differentiation system
Type of Test:	Qualitative Nucleic Acid Amplification Test for *C. difficile* toxin B and binary toxin gene sequences and the single base pair deletion at nucleotide 117 in *tcdC* from unformed stool specimens.
Classification:	I
Classification name:	Device reagents, Clostridium difficile toxin; microorganism differentiation and identification device.
Regulation number:	866.2660
Procode:	LLH, OMN
Classification Advisory Committee:	Microbiology
Panel:	83
Predicate Devices:	Cepheid Xpert® *C. difficile* [510(k) #K001109] BD GeneOhm™ Cdiff Assay [510(k) #K081920]

Device Description:

The Cepheid Xpert *C. difficile/Epi* Assay is a rapid, automated *in vitro* diagnostic test for qualitative detection of toxin producing *Clostridium difficile* directly from unformed (liquid or soft) stool specimens of patients suspected of having *Clostridium difficile* infection (CDI). The assay detects the toxin B gene (*tcdB*), the binary toxin gene (CDT), and the single base pair deletion at nucleotide 117 within the gene encoding a negative regulator of toxin production (*tcdC*Δ117). The combined presence of the genes encoding toxin B and binary toxin and the *tcdC*Δ117 deletion have been associated with a

hypervirulent *C. difficile* strain known as 027/NAP1/BI, which has been associated with severe disease outbreaks in healthcare facilities worldwide. The assay is performed on the Cepheid GeneXpert Dx System.

The Xpert *C. difficile/Epi* Assay system performs sample preparation and real-time, multiplex polymerase chain reaction (PCR) for detection of target-specific DNA.

The GeneXpert Dx System consists of a GeneXpert® instrument, personal computer, and disposable fluidic cartridges. Each instrument contains 1-16 randomly accessible modules that are each capable of performing separate sample preparation and real-time PCR tests for detection of *C. difficile* toxin B and binary toxin gene sequences, and the *tcdC*Δ117 deletion, in less than 45 minutes. Each module contains a syringe drive for dispensing fluids, an ultrasonic horn for lysing cells or spores, and I-CORE® thermocycler for performing real-time PCR and detection.

A swab is inserted into the stool specimen and then is placed in a tube containing elution reagent. Following brief vortexing, the eluted material and two single-use reagents (Reagent 1 and Reagent 2) that are provided with the Assay are transferred to different, uniquely-labeled chambers of the disposable fluidic cartridge (the Xpert *C. difficile/Epi* cartridge). The user initiates a test from the system user interface and places the cartridge into the GeneXpert Dx System instrument platform, which performs hands-off real-time, multiplex polymerase chain reaction (PCR) for detection of DNA. In this platform, additional sample preparation, amplification, and real-time detection are all fully-automated and completely integrated.

The Xpert *C. difficile/Epi* Assay includes reagents for the detection of toxigenic *C. difficile* and the presumptive detection of sequences found in 027/NAP1/BI strains. In addition, the assay reagents include an internal sample processing control (SPC) to ensure adequate processing of the target bacteria and to monitor the presence of inhibitor(s) in the PCR Assay. The SPC also ensures that the PCR conditions (temperature and time) are appropriate for the amplification reaction and that the PCR reagents are functional. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

Device Intended Use:

The Cepheid Xpert® *C. difficile/Epi* Assay is a qualitative *in vitro* diagnostic test for rapid detection of toxin B gene sequences and for presumptive identification of 027/NAP1/BI strains of toxigenic *Clostridium difficile* from unformed (liquid or soft) stool specimens collected from patients suspected of having *C. difficile* infection (CDI). Presumptive identification of 027/NAP1/BI strains of *C. difficile* is by detection of binary toxin (CDT) gene sequences and the single base pair deletion at nucleotide 117 in the *tcdC* gene. The *tcdC* gene encodes for a negative regulator in *C. difficile* toxin production. The test is performed on the Cepheid GeneXpert® Dx System and utilizes automated real-time polymerase chain reaction (PCR) to detect toxin gene sequences associated with toxin producing *C. difficile*. The Xpert *C. difficile/Epi* Assay is intended

as an aid in the diagnosis of CDI. Detection of 027/NAP1/BI strains of *C. difficile* by the Xpert *C. difficile/Epi* Assay is presumptive and is solely for epidemiological purposes and is not intended to guide or monitor treatment for *C. difficile* infections. Concomitant culture is necessary only if further typing or organism recovery is required.

Substantial Equivalence:

The Xpert *C. difficile/Epi* Assay is substantially equivalent to the Cepheid Xpert *C. difficile* Assay and the BD Diagnostics GeneOhm Cdiff Assay. All three assays qualitatively detect *C. difficile* toxin B gene (*tcdB*) in unformed (liquid or soft) stool specimens and use real-time PCR amplification and fluorogenic target-specific hybridization detection.

Table 5.1 shows the similarities and differences between the Xpert *C. difficile/Epi* Assay and the predicate devices.

The Xpert *C. difficile/Epi* is also substantially equivalent to the *C. difficile* reference culture method followed with strain identification of all *C. difficile* isolates as shown in a multi-center clinical comparison study.

The multi-center clinical comparison study was conducted on 2293 patients to evaluate the performance of the Xpert *C. difficile* Assay relative to the reference culture method and cytotoxin B isolate testing. Following culture testing, the toxigenic *C. difficile* isolates were sent to three central laboratories for strain typing by PCR Ribotyping, PFGE and REA methods for the identification of 027/NAP1/BI hypervirulent strains.

The test results showed the Xpert *C. difficile* Assay to be substantially equivalent to the current standard of care, the *C. difficile* reference culture method followed with strain identification of all toxigenic *C. difficile* isolates.

Table 5.1: Similarities and Differences Between the Xpert *C. difficile/Epi* Assay and the Predicate Devices

	Device	**Predicate**	**Predicate**
Item	**Xpert *C. difficile/Epi* Assay**	**Xpert *C. difficile* Assay (K091109)**	**BD GeneOhm Cdiff Assay (K081920)**
Intended Use	The Cepheid Xpert® *C. difficile/Epi* Assay is a qualitative *in vitro* diagnostic test for rapid detection of toxin B gene sequences and for presumptive identification of 027/NAP1/BI strains of toxigenic *Clostridium difficile* from unformed (liquid or soft) stool specimens collected from patients suspected of having *C. difficile* infection (CDI). Presumptive identification of 027/NAP1/BI strains of *C. difficile* is by detection of binary toxin (CDT) gene sequences and the single base pair deletion at nucleotide 117 in the *tcdC gene.* The *tcdC* gene encodes for a negative regulator in *C. difficile* toxin production. The test is performed on the Cepheid GeneXpert® Dx System and utilizes automated real-time polymerase chain reaction (PCR) to detect toxin gene sequences associated with toxin producing *C. difficile*. The Xpert *C. difficile/Epi* Assay is intended as an aid in the diagnosis of CDI. Detection of 027/NAP1/BI strains of *C. difficile* by the Xpert *C. difficile/Epi* Assay is presumptive and is solely for epidemiological purposes and is not intended to guide or monitor treatment for *C. difficile* infections. Concomitant culture is necessary only if further typing or organism recovery is required.	The Cepheid Xpert *C. difficile* Assay, performed on the Cepheid GeneXpert® Dx System, is a qualitative in vitro diagnostic test for rapid detection of toxin B gene sequences from unformed (liquid or soft) stool specimens collected from patients suspected of having *Clostridium difficile* infection (CDI). The test utilizes automated real-time polymerase chain reaction (PCR) to detect toxin gene sequences associated with toxin producing *C. difficile*. The Xpert *C. difficile* Assay is intended as an aid in the diagnosis of CDI. Concomitant culture is necessary only if further typing or organism recovery is required.	The BD GeneOhm Cdiff Assay is a rapid in vitro diagnostic test for the direct, qualitative detection of *C. difficile* toxin B gene (*tcdB*) in human liquid or soft stool specimens from patients suspected of having *Clostridium difficile*-associated disease (CDAD). The test, based on real-time PCR, is intended for use as an aid in diagnosis of CDAD. The test is performed directly on the specimen, utilizing polymerase chain reaction (PCR) for the amplification of specific targets and fluorogenic target-specific hybridization probes for the detection of the amplified DNA.

	Device	**Predicate**	**Predicate**
Item	**Xpert *C. difficile/Epi* Assay**	**Xpert *C. difficile* Assay (K091109)**	**BD GeneOhm Cdiff Assay (K081920)**
Indication for Use	Identification of *C. difficile* from patients suspected of having *C. difficile* Infection (CDI).	Same	Same
Techno-logical Principles	Fully-automated nucleic acid amplification (DNA); real-time PCR	Same	Same
Specimen Type	Unformed (liquid or soft) Stool	Same	Same
Test Cartridge	Disposable single-use, multi-chambered fluidic cartridge.	Same as Xpert *C. difficile/Epi* Assay	Disposable single-use PCR tube
DNA Target Sequences	*C. difficile* toxin B, binary toxin and the tcdC deletion nt 117 (tcdCΔ117)	*C. difficile* toxin B only	*C. difficile* toxin B only
Instrument System	Cepheid GeneXpert Dx System	Same as Xpert *C. difficile/Epi* Assay	Cepheid SmartCycler Dx System
Sample Extraction	Self-contained and automated after swab elution and two single-dose reagent additions.	Same as Xpert *C. difficile/Epi* Assay	Manual
Probes	TaqMan® Probes	Same as Xpert *C. difficile/Epi* Assay	Molecular Beacons
Sample Extraction	Automated	Same as Xpert *C. difficile/Epi* Assay	Manual
Rapid test results	Less than 45 minutes to results.	Same as Xpert *C. difficile/Epi* Assay	Approximately 75-90 minutes to results.
Users	Operators with no clinical lab experience to experienced clinical laboratory technologists.	Same/ CLIA Moderate Complexity Laboratory Users	CLIA High Complexity Laboratory Users

Non-Clinical Studies:

Analytical Inclusivity

The analytical inclusivity of the Xpert *C. difficile/Epi* Assay was determined using 13 *Clostridium difficile* strains of different toxinotypes selected to represent the range of genetic diversity found in *C. difficile*. Toxinotypes 0, I, III, IV, V, VI, VIII, IX, X, XII, XIV, XXI, and XXII were tested. All strains were tested in triplicate with 900 CFU/swab. All tested toxinotypes were correctly reported as Toxigenic *C. difficile* positive. In addition, all strains were reported either as 027/NAP1/BI presumptive negative or presumptive positive. In three toxinotypes X, IV and XIV, one to three replicates were incorrectly reported as 027/NAP1/BI presumptive positive, respectively. All other strains were correctly identified as 027/NAP1/BI presumptive positive or negative.

Analytical Sensitivity (Limit of Detection)

Studies were performed to determine the 95% confidence intervals for the analytical limit of detection (LoD) of *C. difficile* diluted into a fecal matrix of human origin that can be detected by the Xpert *C. difficile/Epi* Assay. The fecal matrix consisted of human liquid feces (*C. difficile* negative by Xpert *C. difficile/Epi* Assay) diluted in PBS with 15% glycerol. The LoD is defined as the lowest number of colony forming units (CFU) per swab that can be reproducibly distinguished from negative samples with 95% confidence.

Replicates of 20 were evaluated at each *C. difficile* concentration tested (CFU/swab) for 7 different *C. difficile* strains representing toxinotypes 0 (two strains), III (two strains), IV, V and VIII (one of each strain).

The estimate and confidence intervals were determined using logistic regression with data (number of positive results per number of replicates at each level) over the range of CFU loadings. The confidence intervals were determined using maximum likelihood estimates on the logistic model parameters using the large sample variance-covariance matrix. The LoD point estimates and 95% upper and lower confidence intervals for each *C. difficile* toxinotype tested are summarized in Table 5.2.

Table 5.2: 95% Confidence Intervals for Analytical LoD – *C. difficile*

Strain ID	Toxinotype	$LoD_{95\%}$ (CFU/swab)	Lower 95% CI	Upper 95% CI
VPI 10463 (CCUG19126)	0	255	190	632
90556-M6S (ATCC9689)	0	460	419	587
LUMC-1 (027/NAP1/BI)	III	23	19	31
LUMC-5 (027/NAP1/BI)	III	75	45	176
LUMC-7	V	45	34	104
LUMC-6	VIII	60	50	74
9101	XII	41	34	49

The results of this study indicate that the Xpert *C. difficile/Epi* Assay will produce a positive *C. difficile* result 95% of the time for a fecal sample containing 460 CFU/swab and a presumptive positive 027/NAP1/BI result 95% of the time for a swab containing 75 CFU.

In addition to the LoD determination, eighteen *C. difficile* strains representing toxinotypes 0 plus 12 variant toxinotypes, including four 027/NAP1/BI toxinotype III isolates, were tested using the Xpert *C. difficile/Epi* Assay. *C. difficile* strains were selected to broadly represent the majority of *C. difficile* toxinotypes encountered in practice. Stock cultures were prepared by suspending the bacterial growth from agar plates in PBS buffer containing 15% glycerol. The concentration of each stock was adjusted to 1.4-5.9 McFarland units. All strains were serially diluted to approximately 900 CFU/swab and tested in triplicate.

Under the conditions of this study, the Xpert *C. difficile/Epi* Assay correctly identified all 18 strains tested as "Toxigenic *C. diff* POSITIVE". Included in the panel were 8 toxinotypes reported to be positive for binary toxin (CDT) production as well. All were CDT positive using the Xpert *C. difficile/Epi* Assay. All four 027/NAP1/BI isolates representing toxinotype III were correctly identified as "Toxigenic C. diff POSITIVE; 027-NAP1-BI PRESUMPTIVE POSITIVE".

Linearity

A study was conducted to define the reportable range of the Xpert *C. difficile/Epi* Assay and demonstrated a linear relationship.

Analytical Specificity

Fifty-five (55) strains were collected, quantitated and tested using the Xpert *C. difficile/Epi* Assay. The strains originated from the American Type Culture Collection (ATCC), Culture Collection University of Göteborg (CCUG), German Collection of Microorganisms and Cell Cultures (DSMZ), the Centers for Disease Control and Prevention (CDC), the Institute of Public Health, Maribor, Slovenia and Swedish Institute for Infectious Disease Control (SMI).

Of the tested species, ten (10) non-toxigenic *C. difficile* strains and eleven (11) non *C. difficile* Clostridium species were included. The organisms tested were identified as either Gram positive (37) or Gram negative (18). The organisms were further classified as aerobic (24), anaerobic (29) or microaerophilic (2).

Each strain was tested in triplicate at concentrations ranging from $1.1x10^8$ to $2.2x10^{10}$. Positive and negative controls were included in the study. Under the conditions of the study, all isolates were reported "Toxigenic *C. diff* NEGATIVE; 027/NAP1/BI PRESUMPTIVE NEG". The analytical specificity was 100%.

Interfering Substances

Twenty-one (21) biological and chemical substances occasionally used or found in stool specimens were tested for interference with the Xpert *C. difficile/Epi* Assay. Potentially interfering substances include, but are not limited to, Vagisil cream and zinc oxide paste. The 19 substances listed in Table 5.3 showed no detectable interference with the Xpert *C. difficile/Epi* Assay.

Table 5.3: Substances Tested and Showing No Assay Interference

Substance	Substance
Whole Blood Karolinska University Hospital	K-Y Jelly/Gelée® McNeil-PPC
Mucin (porcine) Sigma	Vaseline Unilever
Kaopectate® Chattem	Dulcolax® Boehringer Ingelheim Pharmaceuticals
Imodium® McNeil-PPC	Preparation H Portable Wipes Wyeth Consumer Healthcare
Pepto-Bismol® Procter & Gamble	Vaginal Contraceptive Film (VCF) Apothecus Pharmaceutical
Preparation H® Wyeth Consumer Healthcare	Vancomycin Fluka
Fleet® CB Fleet Company	Metronidazole Actavis
Fecal fats Karolinska University Hospital	Anusol® Plus TM Warner-Lambert Company
Monistat® McNeil-PPC	E-Z-HD™ High Density Barium Sulfate for suspension E-Z-EM Canada
Hydrocortisone Cream Longs Drugs	

Clinical Studies

Clinical Comparison Study

Performance characteristics of the Xpert *C. difficile/Epi* Assay were determined in a multi-site prospective investigation study at seven US and Canadian institutions by comparing the Xpert *C. difficile/Epi* Assay to reference culture followed by cell cytotoxicity testing on the isolates and strain typing on the toxigenic strains by restriction endonuclease analysis (REA), pulsed-field gel electrophoresis (PFGE), and PCR ribotyping methods.

Subjects included individuals whose routine care called for *C. difficile* testing. A portion of each leftover unformed stool specimen was obtained for testing by the Xpert *C. difficile/Epi* Assay. The remaining excess specimen was sent to a central laboratory for reference culture and cytotoxin B isolate testing. Each stool specimen was inoculated onto pre-reduced CCFA-D (cycloserine-cefoxitin-fructose agar –direct plate) and Cycloserine cefoxitin mannitol broth with taurocholate lysozyme cysteine (CCMB-TAL). After 24 hours the CCMB-TAL was subcultured on to a second CCFA-E plate (CCFA-Enriched). This direct-enriched culture method is referred to hereafter as "reference culture".

If *C. difficile* was isolated from the CCFA-D plate and the isolate was positive by cell cytotoxicity assay, the specimen was classified as "toxigenic *C. difficile* positive" and CCFA-E plate was not further analyzed. If no *C. difficile* was isolated from the CCFA-D plate or if the isolate was negative by cell cytotoxicity assay, the CCFA-E plate was further analyzed.

If CCFA-E was positive for *C. difficile* and the isolate was positive for cell cytotoxicity assay, the specimen was classified as "toxigenic *C. difficile* positive". The specimen was reported as "negative" if CCFA-E was negative for *C. difficile* or the isolate was tested negative by cell cytotoxicity assay.

Following central culture testing, the toxigenic *C. difficile* positive isolates were sent to a second set of central laboratories for strain identification by REA, PFGE and PCR ribotyping.

Performance of the Xpert *C. difficile/Epi* Assay was calculated relative to the results of direct culture with strain typing, for each of the three strain typing methods, and reference culture with strain typing, for each of the three strain typing methods.

Overall Results

A total of 2293 specimens were tested by Xpert *C. difficile/Epi* Assay, culture, and strain typing.

Performance vs. Direct Culture

Relative to direct culture with REA strain typing, the Xpert *C. difficile/Epi* Assay demonstrated a sensitivity and specificity for toxigenic *C. difficile* of 98.72% and 90.86%, respectively. The Xpert *C. difficile/Epi* Assay also demonstrated 98.55% positive agreement and 97.65% negative agreement for BI (Table 5.4).

Table 5.4: Xpert *C. difficile/Epi* Assay Performance vs. Direct Culture & REA

		Direct Culture & REA			
Xpert *C. diff/Epi*[a]		Toxin B + BI +	Toxin B + BI –	NEG	Total[b]
	Toxin B + 027/NAP1/BI +	68	5	47	120
	Toxin B + 027/NAP1/BI –	1	158	140	299
	NEG	0	3	1860	1863
	Total	69	166	2047	2282
		Toxigenic *C. difficile*		Toxigenic *C. difficile* / 027/NAP1/BI	
		Sensitivity:	98.72% (232/235)	Pos Agreement:	98.55% (68/69)
		Specificity:	90.86% (1860/2047)	Neg Agreement:	97.65% (2161/2213)
		Accuracy:	91.67% (2092/2282)	Accuracy:	97.68% (2229/2282)
		PPV[c]:	55.37% (232/419)	PPV:	56.67% (68/120)
		NPV[d]:	99.84% (1860/1863)	NPV:	99.95% (2161/2162)

[a] Xpert results shown are for first or second attempt. Approximately 3.2% of the specimens were indeterminate on the first attempt.

[b] 11 specimens were culture positive but were not strain typed for the following reasons: incomplete restriction endonuclease digestion; or the isolate was not sent. These 11 specimens are not included in the performance characteristics above.

[c] Positive predictive value

[d] Negative predictive value

Relative to direct culture with PFGE strain typing, the Xpert *C. difficile/Epi* Assay demonstrated a sensitivity and specificity for toxigenic *C. difficile* of 98.76% and 90.86%, respectively. The Xpert *C. difficile/Epi* Assay also demonstrated 100% positive agreement and 97.61% negative agreement for NAP1 (Table 5.5).

Table 5.5: Xpert *C. difficile/Epi* Assay Performance vs. Direct Culture & PFGE

		Direct Culture & PFGE			
Xpert *C. diff/Epi*[a]		Toxin B + NAP1 +	Toxin B + NAP1 –	NEG	Total[b]
	Toxin B +; 027/NAP1/BI +	71	6	47	124
	Toxin B +; 027/NAP1/BI –	0	161	140	301
	NEG	0	3	1860	1863
	Total	71	169	2047	2288
		Toxigenic *C. difficile*		Toxigenic *C. difficile* / 027/NAP1/BI	
		Sensitivity:	98.76% (238/241)	Pos Agreement:	100% (71/71)
		Specificity:	90.86% (1860/2047)	Neg Agreement:	97.61% (2163/2216)
		Accuracy:	91.70% (2098/2288)	Accuracy:	97.68% (2234/2288)
		PPV[c]:	56.00% (238/425)	PPV:	57.26% (71/124)
		NPV[d]:	99.84% (1860/1863)	NPV:	100% (2164/2164)

[a] Xpert results shown are for first or second attempt. Approximately 3.2% of the specimens were indeterminate on the first attempt.

[b] 5 specimens were culture positive but were not strain typed for the following reasons: incomplete restriction endonuclease digestion; no growth; or contamination. These 5 specimens are not included in the performance characteristics above.

[c] Positive predictive value

[d] Negative predictive value

Relative to direct culture with PCR ribotyping, the Xpert *C. difficile/Epi* Assay demonstrated a sensitivity and specificity for toxigenic *C. difficile* of 98.78% and 90.86%, respectively. The Xpert *C. difficile/Epi* Assay also demonstrated 100% positive agreement and 97.70% negative agreement for 027 (Table 5.6).

Table 5.6: Xpert *C. difficile/Epi* Assay Performance vs. Direct Culture & PCR Ribotyping

		Direct Culture & PCR-Ribotyping			
Xpert *C. diff/Epi*[a]		Toxin B + 027+	Toxin B + 027 –	NEG	Total[b]
	Toxin B +; 027/NAP1/BI +	74	4	47	125
	Toxin B +; 027/NAP1/BI –	0	164	140	304
	NEG	0	3	1860	1863
	Total	74	171	2047	2292
		Toxigenic *C. difficile*		Toxigenic *C. difficile* / 027/NAP1/BI	
		Sensitivity:	98.78% (242/245)	Pos Agreement:	100% (74/74)
		Specificity:	90.86% (1860/2047)	Neg Agreement:	97.70% (2167/2218)
		Accuracy:	91.71% (2102/2292)	Accuracy:	97.77% (2241/2292)
		PPV[c]:	56.41% (242/429)	PPV:	59.20% (74/125)
		NPV[d]:	99.84% (1860/1863)	NPV:	100% (2218/2218)

[a] Xpert results shown are for first or second attempt. Approximately 3.2% of the specimens were indeterminate on the first attempt.
[b] One isolate was not typeable due to contamination; this specimen is not included in the performance statistics.
[c] Positive predictive value
[d] Negative predictive value

Performance vs. Reference Culture

Reference (enriched) culture is a more sensitive method for detection of *C. difficile* in symptomatic patients, for example it allows detection of low number of organism due to prior antibiotic treatment and potential loss of viability due to specimen transport.

Relative to reference culture with REA strain typing, the Xpert *C. difficile/Epi* Assay demonstrated a sensitivity and specificity for toxigenic *C. difficile* of 93.35% and 94.02%, respectively. The Xpert *C. difficile/Epi* Assay also demonstrated 96.51% positive agreement and 98.31% negative agreement for BI (Table 5.7).

Table 5.7: Xpert *C. difficile/Epi* Assay Performance vs. Reference Culture & REA

		Reference Culture & REA			
Xpert *C. diff/Epi*[a]		Toxin B + BI +	Toxin B + BI –	NEG	Total[b]
	Toxin B +; 027/NAP1/BI +	83	6	31	120
	Toxin B +; 027/NAP1/BI –	2	204	86	292
	NEG	1	20	1841	1862
	Total	86	230	1958	2274
		Toxigenic *C. difficile*		Toxigenic *C. difficile* / 027/NAP1/BI	
		Sensitivity:	93.35% (295/316)	Pos Agreement:	96.51% (83/86)
		Specificity:	94.02% (1841/1958)	Neg Agreement:	98.31% (2151/2188)
		Accuracy:	93.93% (2136/2274)	Accuracy:	98.24% (2234/2274)
		PPV[c]:	71.60% (295/412)	PPV:	69.17% (83/120)
		NPV[d]:	98.87% (1841/1862)	NPV:	99.86% (2151/2154)

[a] Xpert results shown are for first or second attempt. Approximately 3.3% of the specimens were indeterminate on the first attempt.

[b] 19 specimens were culture positive but were not strain typed for the following reasons: incomplete restriction endonuclease digestion; or the isolate was not sent. These 19 specimens are not included in the performance characteristics above.

[c] Positive predictive value

[d] Negative predictive value

Relative to reference culture with PFGE strain typing, the Xpert *C. difficile/Epi* Assay demonstrated a sensitivity and specificity for toxigenic *C. difficile* of 93.60% and 94.02%, respectively. The Xpert *C. difficile/Epi* Assay also demonstrated 97.73% positive agreement and 98.27% negative agreement for NAP1 (Table 5.8).

Table 5.8: Xpert *C. difficile/Epi* Assay Performance vs. Reference Culture & PFGE

		Reference Culture & PFGE			
Xpert *C. diff/Epi*[a]		Toxin B + NAP1 +	Toxin B +– NAP1 –	NEG	Total[b]
	Toxin B +; 027/NAP1/BI +	86	7	31	124
	Toxin B +; 027/NAP1/BI –	1	213	86	300
	NEG	1	20	1841	1862
	Total	88	240	1958	2286
		Toxigenic *C. difficile*		Toxigenic *C. difficile* / 027/NAP1/BI	
		Sensitivity:	93.60% (307/328)	Pos Agreement:	97.73% (86/88)
		Specificity:	94.02% (1841/1958)	Neg Agreement:	98.27% (2160/2198)
		Accuracy:	93.96% (2148/2286)	Accuracy:	98.25% (2246/2286)
		PPV[c]:	72.41% (307/424)	PPV:	69.35% (86/124)
		NPV[d]:	98.87% (1841/1862)	NPV:	99.91% (2160/2162)

[a] Xpert results shown are for first or second attempt. Approximately 3.2% of the specimens were indeterminate on the first attempt.

[b] 7 specimens were culture positive but were not strain typed for the following reasons: incomplete restriction endonuclease digestion; no growth; or contamination. These 11 specimens are not included in the performance characteristics above.

[c] Positive predictive value

[d] Negative predictive value

Relative to reference culture with PCR ribotyping, the Xpert *C. difficile* Assay demonstrated a sensitivity and specificity for toxigenic *C. difficile* of 93.39% and 94.02%, respectively. The Xpert *C. difficile* Assay also demonstrated 98.89% positive agreement and 98.36% negative agreement for 027 (Table 5.9).

Table 5.9: Xpert *C. difficile* Assay Performance vs. Reference Culture & PCR-Ribotyping

		Reference Culture & PCR-Ribotyping			
Xpert *C. diff/Epi*[a]		Toxin B + 027+	Toxin B + 027 –	NEG	Total[b]
	Toxin B +; 027/NAP1/BI +	89	5	31	125
	Toxin B +; 027/NAP1/BI -	0	217	86	303
	NEG	1	21	1841	1863
	Total	90	243	1958	2291
		Toxigenic *C. difficile*		Toxigenic *C. difficile* / 027/NAP1/BI	
		Sensitivity:	93.39% (311/333)	Pos Agreement:	98.89% (89/90)
		Specificity:	94.02% (1841/1958)	Neg Agreement:	98.36% (2165/2201)
		Accuracy:	93.93% (2152/2291)	Accuracy:	98.38% (2254/2291)
		PPV[c]:	72.66% (311/428)	PPV:	71.20% (89/125)
		NPV[d]:	98.82% (1841/1863)	NPV:	99.95% (2165/2166)

[a] Xpert results shown are for first or second attempt. Approximately 3.2% of the specimens were indeterminate on the first attempt.
[b] 2 specimens were culture positive but were not strain typeable due to contamination and are not included in the performance characteristics above.
[b]Positive predictive value
[c]Negative predictive value

Antibiotic Usage

Among the 2293 cases included in the main dataset, antibiotic use within the 2 months prior to sample collection was reported for 1630 and no antibiotic use was confirmed for 570; for 93 cases, antibiotic status was unknown. Antibiotic use did not cause a statistically significant difference in assay performance.

Reproducibility

Reproducibility of the Xpert *C. difficile/Epi* Assay was demonstrated using a panel of 7 specimens with varying concentrations of a toxigenic *C. difficile* strain, a toxigenic *C. difficile* 027/NAP1/BI strain and a negative that were tested in duplicate on 10 different days at each of the three sites (7 specimens x 2 times/ day x 10 days x 3 sites). One lot of Xpert *C. difficile* kit was used at each of the 3 testing sites. Xpert *C. difficile/Epi* Assays were performed according to the Xpert *C. difficile/Epi* procedure.

A panel of 7 specimens with varying concentrations of *C. difficile* and *C. difficile*, 027/NAP1/BI were tested on 10 different days by two different operators at each of the three sites (7 specimens x 2 operators/ day x 10 days x 3 sites). One lot of Xpert *C. difficile/Epi* Assay was used at each of the 3 testing sites. Xpert *C. difficile/Epi* Assays were performed according to the Xpert *C. difficile/Epi* Assay procedure. Results are summarized in Table 5.10.

Table 5.20: Summary of Reproducibility Results (all)

Specimen ID	Site 1	Site 2	Site 3	% Total Agreement by Sample
Negative	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Toxigenic *C. difficile* High Negative	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Toxigenic *C. difficile* Low Positive	100% (20/20)	85% (17/20)	85% (17/20)	90.0% (54/60)
Toxigenic *C. difficile* Moderate Positive	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
027/NAP1/BI High Negative	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
027/NAP1/BI Low Positive	100% (20/20)	95% (19/20)	95% (19/20)	96.7% (58/60)
027/NAP1/BI Moderate Positive	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
% Total Agreement by Site	100% (140/140)	97.1% (136/140)	97.1% (136/140)	98.1% (412/420)

Conclusions

The results of the nonclinical analytical and clinical performance studies summarized above demonstrate that the Xpert *C. difficile/Epi* Assay is as safe, as effective, and performs as well as or better than the predicate devices.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Cepheid
c/o Russel K. Enns, Ph.D.
Senior Vice President, Chief Regulatory Officer
904 Caribbean Drive
Sunnyvale, CA 94089-1189

APR 0 7 2011

Re: K110203

Trade/Device Name:	Xpert® *C. difficile/Epi*
Regulation Number:	21 CFR §866.2660
Regulation Name:	Microorganism differentiation and identification device
Regulatory Class:	Class I
Product Code:	OMN
Dated:	January 21, 2011
Received:	January 24, 2011

Dear Dr. Enns:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to

proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

4.0 Indications for Use Form

510(k) Number (if known): K110203

Device Name: Xpert® *C. difficile/Epi* Assay

Indications for Use:

The Cepheid Xpert® *C. difficile/Epi* Assay is a qualitative *in vitro* diagnostic test for rapid detection of toxin B gene sequences and for presumptive identification of 027/NAP1/BI strains of toxigenic *Clostridium difficile* from unformed (liquid or soft) stool specimens collected from patients suspected of having *C. difficile* infection (CDI). Presumptive identification of 027/NAP1/BI strains of *C. difficile* is by detection of binary toxin (CDT) gene sequences and the single base pair deletion at nucleotide 117 in the *tcdC* gene. The *tcdC* gene encodes for a negative regulator in *C. difficile* toxin production. The test is performed on the Cepheid GeneXpert® Dx System and utilizes automated real-time polymerase chain reaction (PCR) to detect toxin gene sequences associated with toxin producing *C. difficile*. The Xpert *C. difficile/Epi* Assay is intended as an aid in the diagnosis of CDI. Detection of 027/NAP1/BI strains of *C. difficile* by the Xpert *C. difficile/Epi* Assay is presumptive and is solely for epidemiological purposes and is not intended to guide or monitor treatment for *C. difficile* infections. Concomitant culture is necessary only if further typing or organism recovery is required.

Prescription Use ___X____ (Part 21 CFR 801 Subpart D)	AND/OR	Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) K110203